UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,463	04/05/2001	Nobuto Yamamoto	Y1004/20017	2419

3000 7590 08/24/2004

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.
11TH FLOOR, SEVEN PENN CENTER
PHILADELPHIA, PA 19103-2212

EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/826,463
Filing Date: April 05, 2001
Appellant(s): YAMAMOTO, NOBUTO

Robert S. Silver
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06/30/2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. The statement does not identify any related appeals and interferences. However, claims of a scope similar to the presently claimed invention were rejected under 35 U.S.C. 103(a) in Appellant's predecessor U. S. Application No. 08/618,485 and that rejection was affirmed after appeal before the board of patent appeals and interferences. A copy of decision on appeal in appeal no. 1999-1389 is attached to the examiner's answer.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

There is only one claim on appeal.

(8) Claims Appealed

A substantially correct copy of appealed claim 22 appears on page 1 of the Appendix to the appellant's brief. The minor errors are as follows:

1. "clones" (line 6) should be "cloned"
2. "a molecular weight ... 3 distinct domains" (lines 6-7) should be deleted
3. "bets" (line 8) should be "beta"

(9) Prior Art of Record

5,177,002	Yamamoto	1-1995
5,516,657	Murphy et al.	5-1996
5,652,352	Lichenstein et al.	7-1997

Cooke NE, David EV. Serum vitamin D-binding protein is a third member of the albumin and Alpha fetoprotein gene family. J Clin Invest. 1985 Dec;76(6):2420-4.

Luckow, V.A. "Protein Production and Processing From Baculaovirus Expression Vectors," Chapter 4, In, Baculovirus Expression Systems and Biopesticides, editors, Michael L. Shuler et al. Publication date February 1, 1995. Pages 51-90.

Quirk et al. Production of recombinant human serum albumin from Saccharomyces cerevisiae. Biotechnol Appl Biochem. 1989 Jun;11(3):273-87.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 22 is rejected under 35 U.S.C. 103(a). This rejection is set forth in a prior Office Action, mailed on 03/17/2004, and is reproduced below:

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (A) (U. S. Patent No. 5,177,002) in view of Cooke (U) (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (U) (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (A) (U. S. Patent No. 5,652,352), Murphy (B) (U. S. Patent No. 5,516,657), and Luckow (V).

Yamamoto teaches a process of converting glycosylated Gc protein (Gc1 isoform) to a highly potent macrophage activating factor (GcMAF) by contacting Gc protein with immobilized β-galactosidase and sialidase (Example 2, columns 9-10; paragraph bridging columns 2-3; column 4, full paragraph 2; paragraph bridging columns 4-5). The innermost sugar of the oligosaccharide moiety of Gc1 protein is N-acetylgalactosamine. Treatment of Gc1 protein with endo-N-acetylglucosaminidase, which results in the cleavage of the N-acetylgalactosamine, results in a molecule which cannot be then converted to macrophage activating factor (column 5, full paragraph 1). The macrophage activating factor is believed to comprise a protein in substantially pure form having substantially the amino acid sequence of human group specific component, and a terminal O-linked N-acetylgalactosamine group (column 5, full paragraph 3). The Gc protein has a molecular weight of about 52,000 (sentence bridging columns 1-2) and comprises approximately 458 amino acids, as indicated in Figures 1 and 2. The Gc protein has a molecular weight of about 52,000, comprises approximately 458 amino acids, and has three

distinct domains, as evidenced by Cooke (Figure 3; page 2423, paragraph bridging left and right columns).

The Gc protein is purified from human blood (column 5, full paragraph 5).

The Gc protein is also known as "vitamin-D binding protein" (paragraph bridging columns 1-2). Yamamoto refers to Cooke for nucleotide and amino acid sequences of Gc protein (paragraph bridging columns 1-2).

Yamamoto does not teach, in the sense that Yamamoto does not anticipate, Gc protein obtained via recombinant DNA technology and its conversion to GcMAF.

The concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology. See Quirk, page 273, last full paragraph. Material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity. See Quirk, paragraph bridging pages 273-274.

Cooke discloses a cDNA encoding the human vitamin D-binding protein (hDBP) and its nucleotide and amino acid sequence (page 2421, Figure 2). Comparison of the sequence of the hDBP mRNA and protein to existing protein and nucleic acid data banks demonstrates a strong and highly characteristic homology of the hDBP with human albumin (hALB) and human alpha-fetoprotein (hAFP). Based upon this structural comparison, Cooke establishes that DBP is a member of the ALB and AFP gene family. See the Abstract. Cooke's sequence represents the Gc1 allele (page 2424, left column).

Lichenstein discloses that the human serum proteins albumin (ALB), α-feta-protein (AFP) and vitamin D binding protein (VDB) are known to be members of a multigene ALB family. All three proteins are found in serum. See column 1, lines 10-15. Lichenstein discloses

human afamin (AFM). It shares strong similarity to albumin family members and has the characteristic pattern of disulfide bonds observed in this family. In addition, the gene maps to chromosome 4 as do other members of the albumin gene family. Thus, AFM is the fourth member of the albumin family of proteins. AFM cDNA was stably transfected into Chinese hamster ovary cells and recombinant protein (rAFM) was purified from conditioned medium. column 1, lines 45-65. Host cells from mammals, prokaryotes, fungi, yeast, insects and the like are used for the recombinant expression of AFM (column 13, lines 52-55).

Murphy provides Baculovirus vectors to express recombinant proteins during Baculovirus infection. One advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active. In addition, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems. Although mammalian expression systems result in the production of fully modified, functional protein, yields are often low. E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state. See column 1, lines 40-52. The list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (column 6, full paragraph 3).

Luckow discloses that baculovirus vectors have become widely used to direct the expression of foreign genes. The recombinant proteins are antigenically, immunogenically, and functionally similar to their authentic counterparts (page 51, full paragraph 1). Luckow discloses recombinant baculoviruses and baculovirus vectors (pages 55-66). Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full

paragraphs 2-3). Expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (page 83, last full paragraph).

Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach, in the sense that Cooke, Quirk, Lichenstein, Murphy, and Luckow do not anticipate, Gc protein obtained via recombinant DNA technology and its conversion to GcMAF.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to purify a Gc1 isoform from blood, contact the purified Gc1 isoform in vitro with immobilized β-galactosidase and sialidase, and obtain GcMAF, as taught by Yamamoto, and to modify that teaching by obtaining the Gc protein via recombinant DNA technology, i.e., cloning a Gc1 isoform into a baculovirus vector and expressing the cloned Gc1 isoform, using the teachings of Cooke, Quirk, Lichenstein, Murphy, and Luckow, with a reasonable expectation of success.

One of ordinary skill in the art would be motivated to make this modification because the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology, material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity, E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state, Gc protein (vitamin D binding protein) is a ALB family member, host cells from insects can used for the recombinant expression of an ALB family member, foreign genes for human blood factors may be inserted into Baculovirus vectors, one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the

expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems, although mammalian expression systems result in the production of fully modified, functional protein, yields are often low, recombinant proteins expressed in baculovirus systems are antigenically, immunogenically, and functionally similar to their authentic counterparts, O-linked glycosylation is known to occur on foreign proteins expressed in insect cells, and expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems. The invention is prima facie obvious over the prior art.

(11) Response to Argument

Appellant argues that there is no reasonable expectation of success, and, therefore, there is no motivation to combine the references. Appellant argues that there is no reasonable expectation of success because the Office has not shown that the successful expression of foreign proteins in insect cells is reasonably predictive of the expression of a Gc protein in insect cells. Based on this reasoning, appellant concludes that one of ordinary skill in the art would not have been motivated to express the Gc protein in insect cells. Appellant's arguments have been fully considered but they are not persuasive.

Firstly, in response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

Secondly, obviousness does not require absolute predictability. It only requires a reasonable expectation of success. The fact that one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active (Murphy, column 1, lines 40-52), that the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (Murphy, column 6, full paragraph 3), that baculovirus vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), that the expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph), and that one of ordinary skill in the art recognizes insect cells can be used for the recombinant expression of an albumin family member (Lichenstein, column 13, lines 52-55), of which the Gc protein is also a member (Cooke, Abstract; Lichenstein, column 1, lines 10-15), provides at least some degree of predictability. Accordingly, the argument that there is no reasonable expectation of success, and, hence, there is no motivation to combine the references does not stand.

Appellant argues that none of the cited references show how to clone [a cDNA encoding] the GcMAFc protein or a substantially analogous protein into a baculovirus vector. Appellant's arguments have been fully considered but they are not persuasive. The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. Obviousness does not require that an express written motivation to combine the references appear in prior art references relied upon. The fact that the Gc protein is purified from

human blood (Yamamoto, column 5, full paragraph 5), that the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology (Quirk, page 273, last full paragraph), that Cooke discloses a cDNA encoding the Gc1 allele of the human vitamin D-binding protein and its nucleotide and amino acid sequence (Cooke, page 2421, Figure 2, and page 2424, left column), that Baculovirus vectors have certain advantages over bacterial and yeast expression vectors and mammalian expression systems (Murphy, column 1, lines 40-52), that the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (column 6, full paragraph 3), that baculovirus vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), and that expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph) would have suggested to and motivated one of ordinary skill in the art to use a baculovirus expression system to obtain the GcMAFc. Furthermore, one of ordinary skill in the art would have expected the production of GcMAFc that could not be achieved with other expression systems, as evidenced by Luckow (page 83, last full paragraph), and one of ordinary skill in the art would have expected to avoid the human viral contamination in GcMAFc purified from blood, as evidenced by Quirk (page 273, last full paragraph).

Appellant's statement that the "Gc protein is a soluble membrane protein is acknowledged." However, Yamamoto discloses that the Gc protein is purified from human

blood (column 5, full paragraph 5), and Lichenstein discloses that the human serum protein vitamin D binding protein (VDB) is found in serum (column 1, lines 10-15),

Appellant's statement that all members of the albumin family are not glycosylated, that serum proteins are not O-glycosylated, and, therefore, Gc protein is unique is acknowledged. However, it is known in the art that MAF (macrophage activating factor) is believed to comprise a protein in substantially pure form having substantially the amino acid sequence of human group specific component and a terminal O-linked N-acetylgalactosamine group (Yamamoto, column 5, full paragraph 3) and that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3).

Appellant argues that some baculovirus infected cells do not produce sialylated proteins efficiently unless they are genetically engineered to do so. Appellant's arguments have been fully considered but they are not persuasive. Firstly, there is nothing in the present specification suggesting that this is a critical or essential feature of appellant's invention. Secondly, the claims do not require a cell that has been genetically engineered to produce sialylated proteins. Thirdly, implicit in appellant's arguments is that baculovirus infected cells do produce sialylated proteins. Fourthly, there is no objective evidence of record that provides any weight to appellant's argument. This argument of counsel does not provide any evidence against which the merits of the present rejection can be judged.

Appellants reliance on Luckow at pages 15-16 is acknowledged. The examiner believes appellant intended to rely on Luckow at page 75. Appellant's arguments have been fully considered but they are not persuasive. Yamamoto discloses that the macrophage activating factor is believed to comprise a protein in substantially pure form having substantially the amino

acid sequence of human group specific component, and a terminal O-linked N-acetylgalactosamine group (column 5, full paragraph 3). Thus, GcMAFc does not encompass a microheterogeneous oligosaccharide structure. In view of Yamamoto teaching contacting Gc protein with glycosidases (Example 2, columns 9-10; paragraph bridging columns 2-3; column 4, full paragraph 2; paragraph bridging columns 4-5), appellant has not explained how the ordinarily skilled artisan would consider any potential microheterogeneity a roadblock to obtaining GcMAFc, using insect cells. Furthermore, obviousness does not require absolute predictability. It only requires a reasonable expectation of success. The fact that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3) provides a reasonable expectation of success.

Appellant's discussion of *Vaeck* is acknowledged. Appellant's arguments have been fully considered but they are not persuasive. Unlike the situation in *Vaeck* wherein the expression of an antibiotic resistance-conferring "marker" gene in cyanobacteria, without more, did not render obvious the expression of unrelated genes in cyanobacteria for unrelated proposes, the present claim is directed to or encompasses the production of a blood protein in a system that is widely used for the production of recombinant proteins that are antigenically, immunogenically, and functionally similar to their authentic counterparts (Luckow, page 51, full paragraph 1). Furthermore, the prior suggest the expression of a related blood protein (AFM) in insect cells (Lichenstein, column 13, lines 52-55). Still further, one of ordinary skill in the art would be motivated to use a baculovirus expression system because the Gc protein is purified from human blood (Yamamoto, column 5, full paragraph 5), the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via

recombinant DNA technology (Quirk, page 273, last full paragraph), one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active (Murphy, column 1, lines 40-52), the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (Murphy, column 6, full paragraph 3), baculovirus vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), and expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph). The examiner concludes that the situation in *Vaeck* is not applicable to the present situation.

Appellant argues that none of the cited references make the distinction between a immunogenic (anaphylactic), mutant GcMAFc and the native GcMAFc. Appellant's arguments have been fully considered but they are not persuasive. In response to Appellant's argument that the references fail to show certain features of Appellant's invention, it is noted that the features upon which Appellant relies (i.e., non-immunogenic, non-anaphylactic, and native) are not recited in the rejected claim(s). All that the claim requires is obtaining GcMAFc, and, as acknowledged by appellant (sentence bridging pages 7-8 of the appeal brief), even these potential mutant forms of the Gc protein, if they did occur, would become functional GcMAFc after treatment with glycosidases.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

David S Romeo
Primary Examiner
Art Unit 1647

DSR
August 20, 2004

Conferees
Brenda Brumback, SPE Art Units 1646/47
Yvonne Eyler, Quality Assurance Specialist

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

YVONNE (BONNIE) EYLER, PH.D.
QUALITY ASSURANCE SPECIALIST

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.
12TH FLOOR, SEVEN PENN CENTER
1635 MARKET STREET
PHILADELPHIA, PA 19103-2212

Attachments:
Decision by the BPAI on appeal in appeal no. 1999-1389.